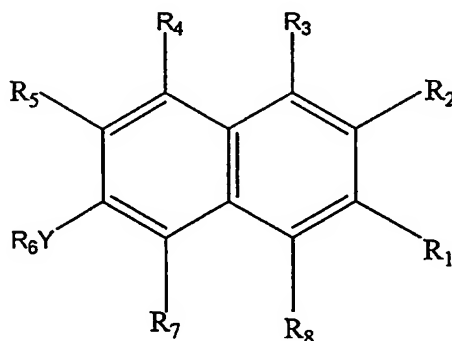


- 114 -

CLAIMS:

1. A method of inhibiting cytokine or biological activity of MIF comprising contacting MIF with a cytokine or biological activity inhibiting effective amount of a
 5 compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof



wherein

10

Y is O, NR₉ or S(O)_q,

- R₁ is selected from hydrogen, C₁₋₆alkyl, -(CR₁₀R_{10'})_nhalo, -(CR₁₀R_{10'})_nOR₁₁,
 -(CR₁₀R_{10'})_n-SR₁₁, -(CR₁₀R_{10'})_n-N(R₁₂)₂, -(CR₁₀R_{10'})_nS(O)R₁₁, -(CR₁₀R_{10'})_nS(O)₂R₁₁,
 15 -(CR₁₀R_{10'})_n-S(O)₃R₁₁, -(CR₁₀R_{10'})_nC(O)R₁₃, -(CR₁₀R_{10'})_n-C(=NR₁₄)R₁₅ or -(CR₁₀R_{10'})_nR₁₆;

R₂ is selected from hydrogen, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, -(CR₁₀R_{10'})_mOR₁₇,
 -(CR₁₀R_{10'})_mSR₁₇, -(CR₁₀R_{10'})_mNR₁₈R₁₉, -(CR₁₀R_{10'})_mS(O)R₂₀, -(CR₁₀R_{10'})_mS(O)₂R₂₀,
 -(CR₁₀R_{10'})_mC(O)R₂₀, -(CR₁₀R_{10'})_mC(S)R₂₀, -(CR₁₀R_{10'})_mC(=NR₁₁)R₁₅ or -(CR₁₀R_{10'})_mR₁₆;

20

R₃, R₄ and R₅ are independently selected from hydrogen, C₁₋₃alkyl, -(CR₁₀R_{10'})_nN(R₁₄)₂,
 -(CR₁₀R_{10'})_nOR₁₄, -(CR₁₀R_{10'})_nSR₁₄ or -(CR₁₀R_{10'})_nhalo;

- R₆ is selected from hydrogen, C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -C(O)N(R₉)₂, -C(S)N(R₉)₂,
 25 -(CR₁₀R_{10'})_nR₂₁, or R₆Y and R₅ together may form -X-(CH₂)_t-Z-, where X and Z may be
 independently selected from O, S or NR₁₄;

- 115 -

R₇ and R₈ are independently selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl or -(CR₁₀R_{10'})_nR₂₂;

5 Each R₉ is independently selected from H or C₁₋₆alkyl;

Each R₁₀ and R_{10'} is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halogen, OR₁₁, SR₁₁, C₁₋₃alkoxy, CO₂R₁₄, N(R₁₄)₂, -CN, NO₂, aryl or heterocyclyl;

10

R₁₁ is hydrogen or C₁₋₆alkyl;

Each R₁₂ is independently selected from hydrogen, C₁₋₆alkyl, NH-C(=NR₁₄)R₁₅, C(O)R₁₄ or C(S)R₁₄;

15

R₁₃ is hydrogen, C₁₋₆alkyl, OR₁₄, SR₁₄ or N(R₁₄)₂;

Each R₁₄ is independently selected from hydrogen or C₁₋₃alkyl;

20 R₁₅ is C₁₋₆alkyl, NH₂, NH(C₁₋₃alkyl) or N(C₁₋₃alkyl)₂, OR₂₃ or SR₂₃;

R₁₆ is hydroxy, C₁₋₃alkoxy, SH, SC₁₋₃alkyl, halo, C(O)R₃₁, C(R₂₄)₃, CN, aryl or heterocyclyl;

25 R₁₇ is selected from hydrogen, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, (CR₂₆R_{26'})_sR₂₇, C(O)R₂₅, CO₂R₂₅, C(S)R₂₅, C(S)OR₂₅, S(O)R₂₅, S(O)₂R₂₅, [C(O)CH(R₂₉)NH]_r-R₂₃ or [sugar]_r;

30 R₁₈ and R₁₉ are independently selected from hydrogen, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, (CR₂₆R_{26'})_sR₂₇, C(O)R₂₅, C(S)R₂₅, S(O)R₂₅, S(O)₂R₂₅, [C(O)CH(R₂₉)NH]_r-R₂₃, [sugar]_r, C(=NR₂₃)NH₂ or NH-C(=NR₂₃)NH₂;

- 116 -

R₂₀ is selected from hydrogen, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, OR₂₈, SR₂₈, N(R₂₈)₂, [NH-CHR₂₉C(O)]_r-OR₂₃, [sugar]_r or (CR₂₆R_{26'})_sR₂₇;

5 R₂₁ is OR₂₈, SR₂₈, halo or N(R₂₅)₂;

R₂₂ is halo, CO₂H, SO₃H, NO₂, NH₂, CO₂C₁₋₃alkyl, SO₃C₁₋₃alkyl or C(R₂₄)₃;

R₂₃ is hydrogen or C₁₋₃alkyl;

10

Each R₂₄ is independently selected from hydrogen, Cl or F;

Each R₂₅ is independently selected from hydrogen, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl, aryl or (CR₂₆R_{26'})_sR₂₇;

15

Each R₂₆ and R_{26'} is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halogen, hydroxy, C₁₋₃alkoxy, CO₂H, CO₂C₁₋₃alkyl, NH₂, NH(C₁₋₃alkyl), N(C₁₋₃alkyl)₂, CN, NO₂, aryl or heteroaryl;

20 R₂₇ is hydroxy, C₁₋₃alkoxy, SH, SC₁₋₃alkyl, halo, NH₂, NH(C₁₋₃alkyl), N(C₁₋₃alkyl)₂, C(O)R₃₁, aryl or heterocyclyl;

Each R₂₈ is independently selected from hydrogen, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, C₂₋₂₀alkynyl or (CR₂₆R_{26'})_sR₃₀;

25

R₂₉ is the characterising group of an amino acid;

R₃₀ is halogen, hydroxy, C₁₋₃alkoxy, NH₂, NH(C₁₋₃alkyl), N(C₁₋₃alkyl)₂, C(O)R₃₁, aryl or heterocyclyl;

30

R₃₁ is C₁₋₃alkyl, OH, C₁₋₃alkoxy, aryl, aryloxy, heterocyclyl or heterocycloxy;

- 117 -

q is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

m is 0 or 1 to 20;

5 r is 1 to 5;

s is 1 to 10; and

t is 1 or 2;

wherein an alkyl, alkenyl, alkynyl, alkyloxy, aryl or heterocyclyl group may be optionally
10 substituted one or more times.

2. A method according to claim 1 wherein Y is O, NH, NC₁₋₆alkyl, or S(O)_q wherein q is 0, 1, 2 or 3.

15 3. A method according to claim 1 wherein R₁ is hydrogen, C₁₋₆alkyl, (CH₂)_nOH, (CH₂)_nNH₂, (CH₂)_nSH, (CH₂)_nCF₃, (CH₂)_nCO₂H, (CH₂)_nCO₂C₁₋₃alkyl, (CH₂)_nC(O)NH₂, (CH₂)_nC(O)NHC₁₋₃alkyl, (CH₂)_nC(O)N(C₁₋₃alkyl)₂, (CH₂)_nSO₃H or (CH₂)_nSO₃C₁₋₃alkyl, where n is 0, 1, 2 or 3.

20 4. A method according to claim 1 wherein R₂ is selected from C₂₋₂₀alkyl, C₁₋₂₀alkenyl, (CR₁₀R_{10'})_mOH, (CR₁₀R_{10'})_mOC₁₋₂₀alkyl, (CR₁₀R_{10'})_mOC₂₋₂₀alkenyl, (CR₁₀R_{10'})_mOC(O)C₁₋₂₀alkyl, (CR₁₀R_{10'})_mOC(O)C₂₋₂₀alkenyl, (CR₁₀R_{10'})_mOC(O)aryl, (CR₁₀R_{10'})_mO[C(O)CH(R₂₉)NH]_r-H, (CR₁₀R_{10'})_mO[sugar]_r, (CR₁₀R_{10'})_mNHC₁₋₂₀alkyl, (CR₁₀R_{10'})_mN(C₁₋₂₀alkyl)₂, (CR₁₀R_{10'})_mNHC₂₋₂₀alkenyl, (CR₁₀R_{10'})_mN(C₂₋₂₀alkenyl)₂,
25 (CR₁₀R_{10'})_mN(C₁₋₂₀alkyl)(C₂₋₂₀alkenyl), (CR₁₀R_{10'})_mNHC(O)C₁₋₂₀alkyl, (CR₁₀R_{10'})_mNHC(O)C₂₋₂₀alkenyl, (CR₁₀R_{10'})_mNHC(O)aryl, (CR₁₀R_{10'})_mNH[C(O)CH(R₂₉)NH]_r-H, (CR₁₀R_{10'})_mNH-[sugar]_r, (CR₁₀R_{10'})_mSO₃H, (CR₁₀R_{10'})_mSO₃C₁₋₂₀alkyl, (CR₁₀R_{10'})_mSO₃C₂₋₂₀alkenyl, (CR₁₀R_{10'})_mC(O)C₁₋₂₀alkyl, (CR₁₀R_{10'})_mC(O)C₂₋₂₀alkenyl, (CR₁₀R_{10'})_mCO₂H, (CR₁₀R_{10'})_mCO₂C₁₋₂₀alkyl,
30 (CR₁₀R_{10'})_mCO₂C₂₋₂₀alkenyl, (CR₁₀R_{10'})_mC(O)NHC₁₋₂₀alkyl, (CR₁₀R_{10'})_mC(O)N(C₁₋₂₀alkyl)₂, (CR₁₀R_{10'})_mC(O)NHC₂₋₂₀alkenyl, (CR₁₀R_{10'})_mC(O)N(C₂₋₂₀alkenyl)₂,

- 118 -

$(\text{CR}_{10}\text{R}_{10'})_m\text{C}(\text{O})\text{N}(\text{C}_{1-20}\text{alkyl})(\text{C}_{2-20}\text{alkenyl})$, $(\text{CR}_{10}\text{R}_{10'})_m\text{C}(\text{O})[\text{NHCH}(\text{R}_{29})\text{C}(\text{O})]_r\text{-OH}$,
 $(\text{CR}_{10}\text{R}_{10'})_m\text{C}(\text{O})[\text{sugar}]_r$, $(\text{CR}_{10}\text{R}_{10'})_m\text{halo}$, $(\text{CR}_{10}\text{R}_{10'})_m\text{CN}$, $(\text{CR}_{10}\text{R}_{10'})_m\text{heterocyclyl}$,
 $(\text{CR}_{10}\text{R}_{10'})_m\text{aryl}$, $(\text{CR}_{10}\text{R}_{10'})_m\text{NHC}(=\text{NH})\text{NH}_2$, $(\text{CR}_{10}\text{R}_{10'})_m\text{SO}_2\text{NHC}_{1-20}\text{alkyl}$,
 $(\text{CR}_{10}\text{R}_{10'})_m\text{C}(\text{O})\text{O}(\text{CH}_2)_{1-10}\text{CO}_2\text{H}$ or $(\text{CR}_{10}\text{R}_{10'})_m\text{C}(\text{O})\text{O}(\text{CH}_2)_{1-10}\text{CO}_2\text{C}_{1-3}\text{alkyl}$; wherein
5 each R_{10} and $\text{R}_{10'}$ is independently selected from hydrogen, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$,
 $\text{C}_{2-6}\text{alkynyl}$, halogen, OH, $\text{OC}_{1-6}\text{alkyl}$, CO_2H , $\text{CO}_2\text{C}_{1-3}\text{alkyl}$, NH_2 , $\text{NHC}_{1-3}\text{alkyl}$,
 $-\text{N}(\text{C}_{1-3}\text{alkyl})_2$, CN, NO_2 , aryl or heterocyclyl; R_{29} is the characterising group of an amino
acid, m is 0 or an integer from 1 to 20 and r is an integer from 1 to 5;

10 5. A method according to claim 1 wherein R_3 is selected from hydrogen, halo, NH_2 ,
OH, $\text{OC}_{1-3}\text{alkyl}$, SH or $\text{SC}_{1-3}\text{alkyl}$.

6. A method according to claim 1 wherein R_4 is selected from hydrogen, halogen, $\text{C}_{1-3}\text{alkyl}$,
 $(\text{CH}_2)_n\text{NH}_2$, $(\text{CH}_2)_n\text{NHC}_{1-3}\text{alkyl}$, $(\text{CH}_2)_n\text{NH}(\text{C}_{1-3}\text{alkyl})_2$, $(\text{CH}_2)_n\text{OH}$ or $(\text{CH}_2)_n\text{OC}_{1-3}\text{alkyl}$
15 alkyl and n is 0, 1, 2 or 3.

7. A method according to claim 1 wherein R_5 is selected from hydrogen, halogen,
 $(\text{CH}_2)_n\text{NH}_2$, $(\text{CH}_2)_n\text{OH}$, $(\text{CH}_2)_n\text{OC}_{1-3}\text{alkyl}$, $(\text{CH}_2)_n\text{SH}$ or $(\text{CH}_2)_n\text{SC}_{1-3}\text{alkyl}$ and n is 0, 1, 2 or
3.

20

8. A method according to claim 1 wherein R_6 is selected from hydrogen, $\text{C}_{1-3}\text{alkyl}$,
 $\text{C}(\text{O})\text{C}_{1-3}\text{alkyl}$, $\text{C}(\text{O})\text{NH}(\text{C}_{1-3}\text{alkyl})$, $\text{C}(\text{O})\text{N}(\text{C}_{1-3}\text{alkyl})_2$, $\text{C}(\text{S})\text{NH}(\text{C}_{1-3}\text{alkyl})$ or $\text{C}(\text{S})\text{N}(\text{C}_{1-3}\text{alkyl})_2$.

25 9. A method according to claim 1 wherein R_5 and R_6 taken together form $-\text{X}-(\text{CH}_2)_t-$
 Z wherein X and Z are independently selected from O and S and t is 1 or 2.

10. A method according to claim 1 wherein R_7 is selected from hydrogen, $\text{C}_{1-3}\text{alkyl}$,
 $(\text{CH}_2)_n\text{SO}_3\text{H}$, $(\text{CH}_2)_n\text{NO}_2$, $(\text{CH}_2)_n\text{OH}$, $(\text{CH}_2)_n\text{CO}_2\text{H}$, $(\text{CH}_2)_n\text{NH}_2$, $(\text{CH}_2)_n\text{halo}$,
30 $(\text{CH}_2)_n\text{CH}_2\text{halo}$, $(\text{CH}_2)_n\text{CH}(\text{halo})_2$ or $(\text{CH}_2)_n\text{C}(\text{halo})_3$ and n is 0, 1, 2 or 3.

- 119 -

11. A method according to claim 1 wherein R_3 is selected from hydrogen, C_{1-3} alkyl, or $(CH_2)_nR_{22}$, wherein R_{22} is halo, CH_2 halo, $CH(halo)_2$ or $C(halo)_3$ and n is 0, 1, 2 or 3.
12. A method according to claim 1 wherein at least one of R_{10} and $R_{10'}$ in each
5 $(CR_{10}R_{10'})$ is hydrogen.
13. A method according to claim 1 wherein at least one of R_{26} and $R_{26'}$ in each $(CR_{26}R_{26'})$ is hydrogen.
- 10 14. A method according to claim 1 wherein
- Y is O, NR_9 or $S(O)_q$;
- R_1 is hydrogen, C_{1-6} alkyl, $-(CH_2)_nC(O)R_{13}$, $-(CH_2)_nS(O)_3R_{11}$, $-(CH_2)_nNH_2$, $-(CH_2)_nOH$,
15 $-(CH_2)_nSH$ or $-(CH_2)_nCF_3$, where R_{11} and R_{13} are defined in claim 1;
- R_2 is selected from hydrogen, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, $-(CR_{10}R_{10'})_mOR_{17}$,
 $-(CR_{10}R_{10'})_mSR_{17}$, $-(CR_{10}R_{10'})_mNR_{18}R_{19}$, $-(CR_{10}R_{10'})_mS(O)R_{20}$, $-(CR_{10}R_{10'})_mS(O)_2R_{20}$,
 $-(CR_{10}R_{10'})_mC(O)R_{20}$, $-(CR_{10}R_{10'})_mC(S)R_{20}$, $-(CR_{10}R_{10'})_mC(=NR_{11})R_{15}$ or $-(CR_{10}R_{10'})_mR_{16}$,
20 where m , R_{10} , $R_{10'}$, R_{11} , R_{15} , R_{16} , R_{17} , R_{18} , R_{19} , R_{20} are as defined in claim 1;
- R_3 is selected from hydrogen, halo, amino, OH, OC_{1-3} alkyl or SH;
- R_4 is selected from hydrogen, halogen, C_{1-3} alkyl, $(CH_2)_nNH_2$, $(CH_2)_nNHC_{1-3}$ alkyl,
25 $(CH_2)_nNH(C_{1-3}alkyl)_2$, $(CH_2)_nOH$ or $(CH_2)_nOC_{1-3}alkyl$;
- R_5 is selected from hydrogen, halogen, $(CH_2)_nNH_2$, $(CH_2)_nOH$, $(CH_2)_nOC_{1-3}alkyl$,
 $(CH_2)_nSH$ or $(CH_2)_nSC_{1-3}alkyl$;
- 30 R_6 is hydrogen, C_{1-3} alkyl, CH_2 halo, $C(O)NH(C_{1-3}alkyl)$, $C(O)N(C_{1-3}alkyl)_2$, $C(S)NH(C_{1-3}alkyl)$ or $C(S)N(C_{1-3}alkyl)_2$, CH_2OH or CH_2SH ;

- 120 -

or R_5 and YR_6 together form $X-(CH_2)_t-Z$ wherein X and Z are independently selected from O and S ;

- 5 R_7 is selected from hydrogen, C_{1-3} alkyl, or $(CH_2)_nSO_3H$, $(CH_2)_nNO_2$, $(CH_2)_nOH$, $(CH_2)_nCO_2H$, $(CH_2)_nNH_2$, $(CH_2)_nhalo$, $(CH_2)_nCH_2halo$, $(CH_2)_nCH(halo)_2$ or $(CH_2)_nC(halo)_3$,

R_8 is hydrogen, C_{1-3} alkyl or $(CH_2)_nhalo$, and

10

q and n are 0, 1, 2 or 3.

15. A method according to claim 1 wherein

- 15 Y is O , NR_9 or $S(O)_q$;

R_1 is hydrogen, $(CH_2)_nCO_2H$, $(CH_2)_nCO_2C_{1-3}alkyl$, $(CH_2)_nSO_3H$, $(CH_2)_nNH_2$, $C_{1-3}alkyl$, $(CH_2)_nOH$ or $(CH_2)_nCF_3$;

- 20 R_2 is selected from hydrogen, $C_{1-20}alkyl$, $C_{2-20}alkenyl$, $C_{2-20}alkynyl$, $-(CR_{10}R_{10'})_mOR_{17}$, $-(CR_{10}R_{10'})_mSR_{17}$, $-(CR_{10}R_{10'})_mNR_{18}R_{19}$, $-(CR_{10}R_{10'})_mS(O)R_{20}$, $-(CR_{10}R_{10'})_mS(O)_2R_{20}$, $-(CR_{10}R_{10'})_mC(O)R_{20}$, $-(CR_{10}R_{10'})_mC(S)R_{20}$, $-(CR_{10}R_{10'})_mC(=NR_{11})R_{15}$ or $-(CR_{10}R_{10'})_mR_{16}$, where m , R_{10} , $R_{10'}$, R_{11} , R_{15} , R_{16} , R_{17} , R_{18} , R_{19} , R_{20} are as defined in claim 1;

- 25 R_3 is selected from hydrogen, OH or $OC_{1-3}alkyl$,

R_4 is selected from hydrogen, $C_{1-3}alkyl$, $(CH_2)_nNH_2$, $(CH_2)_nOH$ or $(CH_2)_nOC_{1-3}alkyl$;

R_5 is hydrogen, $(CH_2)_nOH$ or $(CH_2)_nOC_{1-3}alkyl$;

30

R_6 is hydrogen, $C_{1-3}alkyl$, CH_2halo , $C(O)NH(C_{1-3}alkyl)$, $C(O)N(C_{1-3}alkyl)_2$, $C(S)NH(C_{1-3}alkyl)$,

- 121 -

alkyl) or C(S)N(C₁₋₃alkyl)₂, CH₂OH or CH₂SH;

or R₅ and R₆ are taken together to form -O-(CH₂)_t-O where t is 1 or 2;

5 R₇ is selected from hydrogen, (CH₂)_nSO₃H, (CH₂)_nNO₂, (CH₂)_nNH₂, or (CH₂)_nhalo

R₈ is hydrogen, CH₃, CF₃ or CCl₃;

and q and n are 0, 1, 2 or 3.

10

16. A method according to claim 1 wherein

Y is O, NR₉ or S(O)_q;

15 R₁ is hydrogen, (CH₂)_nCO₂H, (CH₂)_nCO₂C₁₋₃alkyl, (CH₂)_nSO₃H, (CH₂)_nNH₂, C₁₋₃alkyl, (CH₂)_nOH or (CH₂)_nCF₃;

R₂ is selected from hydrogen, C₁₋₂₀alkyl, C₂₋₂₀alkenyl, -(CR₁₀R_{10'})_mOH, -(CR₁₀R_{10'})_mNHC₁₋₂₀alkyl, -(CR₁₀R_{10'})_mNH[C(O)CH(R₂₉)NH]-H, -(CR₁₀R_{10'})_mSO₃H, -(CR₁₀R_{10'})_mSO₃C₁₋₂₀alkyl, -(CR₁₀R_{10'})_mC(O)C₁₋₂₀alkyl, -(CR₁₀R_{10'})_mCO₂H, -(CR₁₀R_{10'})_mCO₂C₁₋₂₀alkyl, -(CR₁₀R_{10'})_mCN, -(CR₁₀R_{10'})_mhalo, -(CR₁₀R_{10'})_maryl, -(CR₁₀R_{10'})_mheterocyclyl, -(CR₁₀R_{10'})_mNHC(=NH)NH₂, -(CR₁₀R_{10'})_mSO₂NHC₁₋₂₀alkyl, CO₂(CH₂)₁₋₁₀CO₂H or CO₂(CH₂)₁₋₁₀CO₂C₁₋₃alkyl, where m, R₁₀ and R_{10'} are as defined in claim 1;

25 R₃ is selected from hydrogen, OH or OC₁₋₃alkyl,

R₄ is selected from hydrogen, C₁₋₃alkyl, (CH₂)_nNH₂, (CH₂)_nOH or (CH₂)_nOC₁₋₃alkyl;

R₅ is hydrogen, (CH₂)_nOH or (CH₂)_nOC₁₋₃alkyl;

30

R₆ is hydrogen, C₁₋₃alkyl, CH₂halo, C(O)NH(C₁₋₃alkyl), C(O)N(C₁₋₃alkyl)₂, C(S)NH(C₁₋

- 122 -

alkyl) or C(S)N(C₁₋₃alkyl)₂, CH₂OH or CH₂SH;

or R₅ and R₆ are taken together to form -O-(CH₂)_t-O where t is 1 or 2;

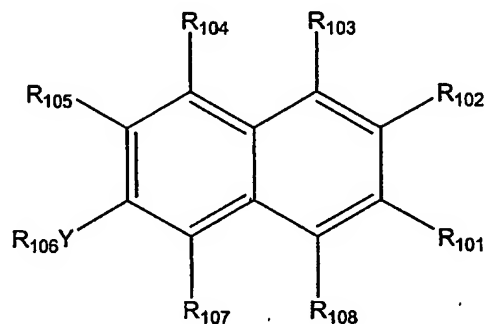
5 R₇ is selected from hydrogen, (CH₂)_nSO₃H, (CH₂)_nNO₂, (CH₂)_nNH₂, or (CH₂)_nhalo;

R₈ is hydrogen, CH₃, CF₃ or CCl₃;

and q and n are 0, 1, 2 or 3.

10

17. A method according to claim 1 wherein the compound of formula (I) is a compound of formula (II):



(II)

15

wherein Y is selected from -O-, -NH-, -NC₁₋₃alkyl- or -S(O)_q-;

R₁₀₁ is selected hydrogen, C₁₋₆alkyl, CO₂H or CO₂C₁₋₆alkyl;

R₁₀₂ is selected from C₁₋₂₀alkyl, C₂₋₂₀alkenyl, CO₂H, CO₂C₁₋₂₀alkyl, CO₂C₂₋₂₀alkenyl,

20 CO₂(CH₂)_mR₁₀₉, SO₃H, SO₃C₁₋₂₀alkyl, SO₃C₂₋₂₀alkenyl, SO₃(CH₂)_mR₁₀₉, C(O)C₁₋₂₀alkyl or (CH₂)_mR₁₁₀;

R₁₀₃ is selected from hydrogen, hydroxy, methoxy or C₁₋₃alkyl;

- 123 -

R₁₀₄ is selected from hydrogen, C₁₋₃alkyl, NH₂, NH(C₁₋₃alkyl), N(C₁₋₃alkyl)₂ or (CH₂)_nOH;

R₁₀₅ is selected from hydrogen, (CH₂)_nOH or (CH₂)_nOC₁₋₃alkyl;

5

R₁₀₆ is selected from hydrogen, C₁₋₃alkyl, C(O)NH₂, C(O)NH(C₁₋₃alkyl), C(O)N(C₁₋₃alkyl)₂, C(S)NH₂, C(S)NH(C₁₋₃alkyl) or C(S)N(C₁₋₃alkyl)₂;

R₁₀₇ is selected from hydrogen, hydroxy, halo, amino, nitro, cyano, SO₃H or CO₂H;

10

R₁₀₈ is selected from hydrogen or methyl;

R₁₀₉ is selected from halogen, hydroxy, C₁₋₃alkoxy, NH₂, NH(C₁₋₃alkyl), N(C₁₋₃alkyl)₂, CO₂H or CO₂C₁₋₃alkyl;

15

R₁₁₀ is selected from hydroxy, C₁₋₃alkyl, halo, CO₂H, CO₂C₁₋₃alkyl, CN, NH₂, NH(C₁₋₃alkyl) or N(C₁₋₃alkyl)₂;

n is 0 or an integer from 1 to 3;

20

m is 0 or an integer from 1 to 20; and

wherein an alkyl, alkenyl or alkyloxy, group may be optionally substituted one or more times.

25

18. A method according to claim 1 wherein the compound of formula (I) is selected from the group consisting of:

6,7-dihydroxy-2-naphthalene

6,7-dimethoxy-2-naphthalene

30

6,7-dimethoxy-2-acetonoaphthone

6,7-Dimethoxy-2-naphthoic acid

- 124 -

- 2-carboxy-6-hydroxynaphthalene-5-sulfonic acid
6,7-dihydroxy-2-naphthalenesulfonic acid
Pentyl 6,7-dihydroxy-2-naphthalenesulfonate
6-hydroxy-2-naphthalenesulfonic acid
5 6-methylamino-2-naphthalenesulfonic acid
2,3-dihydronaphtho[2,3-b][1,4]dioxine-7-carboxylic acid
Methyl 6-hydroxy-2-naphthoate
dodecanyl-6-hydroxy-2-naphthoate
[(6-hydroxy-2-naphthyl)carbonyl]oxyhexanoic acid
10 (6-methoxy-6-oxohexyl)-6-hydroxy-2-naphthoate
6-hydroxy-5-nitro-2-naphthoic acid
Ethyl 1,6-dihydroxy-2-naphthoate
Ethyl 6-[(dimethylamino)carbonyl]sulfanyl-1-methoxy-2-naphthoate
Ethyl 6-hydroxy-1-methoxy-2-naphthoate
15 Ethyl 6-[(dimethylamino)thiocarbonyl]oxy-1-methoxy-2-naphthoate
7-methoxy-3-hydroxy-2-naphthoic acid
Methyl 7-methoxy-3-hydroxy-2-naphthoate
Methyl 7-methoxy-3-methyl-2-naphthoate
7-methoxy-3-methyl-2-naphthoic acid
20 5-bromo-6-methoxy-2-methyl-3-naphthoic acid
6-hydroxy-[2-(1-pentylamino)methyl]-3-naphthoic acid
Methyl 3-bromomethyl-7-hydroxy-2-naphthoate
Methyl 7-methoxy-2-naphthoate
Methyl 7-hydroxy-2-naphthoate
25 Methyl 7-hydroxy-8-nitro-2-naphthoate
Methyl 6-hydroxy-5-nitro-2-naphthoate
Methyl 6-methoxy-5-nitro-2-naphthoate
Methyl 5-amino-6-methoxy-2-naphthoate
Methyl 6-methoxy-2-naphthoate
30 2-hydroxymethyl-6-methoxynaphthalene
2-bromomethyl-6-methoxy-naphthalene

- 125 -

2-cyanomethyl-6-methoxynaphthalene

2-(1-cyano-1-hex-5-enyl)-6-methoxynaphthalene

2-(6-methoxy-2-naphthyl)hept-6-enoic acid

Methyl 2-(6-methoxy-2-naphthyl)hept-6-enoate

5 7-hydroxy-2-(6-methoxy-2-naphthyl)heptanoic acid

Methyl 6-methoxy-8-methyl-2-naphthoate ester

6-hydroxy-2-naphthanoic acid

6-methoxy- α -methyl-2-naphthalene acetic acid

2,6-naphthalene disulfonic acid.

10

19. A method of treating, preventing or diagnosing a disease or condition wherein MIF cytokine or biological activity is implicated comprising the administration of a treatment, prevention or diagnostic effective amount of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof to a subject in need thereof.

15

20. A method according to claim 19 wherein the disease or condition is selected from autoimmune diseases, solid or haemopoietic tumours, or chronic or acute inflammatory diseases.

20

21. A method according to claim 19 wherein the disease or condition selected from the group comprising rheumatic diseases, spondyloarthropathies, crystal arthropathies, Lyme disease, connective tissue diseases, vasculitides, glomerulonephritis, interstitial nephritis, inflammatory bowel disease, peptic ulceration, gastritis, oesophagitis, liver disease, autoimmune diseases, pulmonary diseases, cancers whether primary or metastatic, atherosclerosis, disorders of the hypothalamic-pituitary-adrenal axis, brain disorders, corneal disease, iritis, iridocyclitis, cataracts, uveitis, sarcoidosis, diseases characterised by modified angiogenesis, endometrial function, psoriasis, endotoxic (septic) shock, exotoxic (septic) shock, infective (true septic) shock, other complications of infection, pelvic inflammatory disease, transplant rejection, allergies, allergic rhinitis, bone diseases, atopic dermatitis, UV(B)-induced dermal cell activation, malarial complications, diabetes mellitus, pain, inflammatory consequences of trauma or ischaemia, testicular dysfunctions

30

- 126 -

and wound healing.

22. A method according to claim 21 wherein the disease or condition is selected from the group consisting of rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ankylosing
5 spondylitis, reactive arthritis, Reiter's syndrome, gout, pseudogout, calcium pyrophosphate deposition disease, systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, Sjögren's syndrome, polyarteritis nodosa, Wegener's granulomatosis, Churg-Strauss syndrome, ulcerative colitis, Crohn's disease, cirrhosis, hepatitis, diabetes mellitus, thyroiditis, myasthenia gravis, sclerosing cholangitis, primary biliary cirrhosis,
10 diffuse interstitial lung diseases, pneumoconioses, fibrosing alveolitis, asthma, bronchitis, bronchiectasis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, colon cancer, lymphoma, lung cancer, melanoma, prostate cancer, breast cancer, stomach cancer, leukemia, cervical cancer and metastatic cancer, ischaemic heart disease, myocardial infarction, stroke, peripheral vascular disease, Alzheimer's disease, multiple
15 sclerosis, diabetic retinopathy, parturition, endometriosis, osteoporosis, Paget's disease, sunburn and skin cancer.

23. A method according to claim 19 wherein the subject is a human subject.

20 24. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier, diluent or excipient.

25 25. A pharmaceutical composition according to claim 24 further comprising a glucocorticoid.

26. A method of treating or preventing a disease or condition wherein MIF cytokine or biological activity is implicated comprising administering to a mammal a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof
30 and a second therapeutic agent.

- 127 -

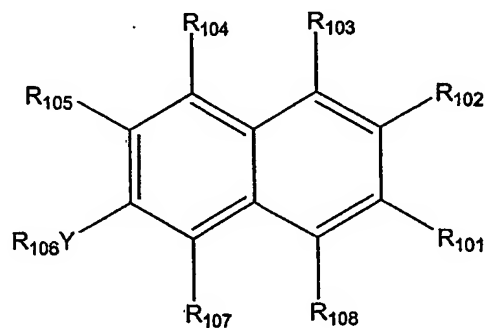
27. A method according to claim 26 wherein the second therapeutic agent is a glucocorticoid.

28. A method of prophylaxis or treatment of a disease or condition for which treatment with a glucocorticoid is indicated, said method comprising administering to a mammal a glucocorticoid and a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof.

29. A method of treating steroid-resistant diseases comprising administering to a mammal a glucocorticoid and a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof.

30. A method of enhancing the effect of a glucocorticoid in mammals comprising administering a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof, simultaneously, separately or sequentially with said glucocorticoid.

31. A compound of formula (II) or a pharmaceutically acceptable salt or prodrug thereof:



(II)

wherein Y is selected from -O-, -NH-, -NC₁₋₃alkyl- or -S(O)_q-;

- 128 -

R₁₀₁ is selected hydrogen, C₁₋₆alkyl, CO₂H or CO₂C₁₋₆alkyl;

R₁₀₂ is selected from C₁₋₂₀alkyl, C₂₋₂₀alkenyl, CO₂H, CO₂C₁₋₂₀alkyl, CO₂C₂₋₂₀alkenyl,
 5 CO₂(CH₂)_mR₁₀₉, SO₃H, SO₃C₁₋₂₀alkyl, SO₃C₂₋₂₀alkenyl, SO₃(CH₂)_mR₁₀₉, C(O)C₁₋₂₀alkyl or
 (CH₂)_mR₁₁₀;

R₁₀₃ is selected from hydrogen, hydroxy, methoxy or C₁₋₃alkyl;

10 R₁₀₄ is selected from hydrogen, C₁₋₃alkyl, NH₂, NH(C₁₋₃alkyl), N(C₁₋₃alkyl)₂ or (CH₂)_nOH;

R₁₀₅ is selected from hydrogen, (CH₂)_nOH or (CH₂)_nOC₁₋₃alkyl;

R₁₀₆ is selected from hydrogen, C₁₋₃alkyl, C(O)NH₂, C(O)NH(C₁₋₃alkyl), C(O)N(C₁₋₃alkyl)₂,
 15 C(S)NH₂, C(S)NH(C₁₋₃alkyl) or C(S)N(C₁₋₃alkyl)₂;

R₁₀₇ is selected from hydrogen, hydroxy, halo, amino, nitro, cyano, SO₃H or CO₂H;

R₁₀₈ is selected from hydrogen or methyl;

20

R₁₀₉ is selected from halogen, hydroxy, C₁₋₃alkoxy, NH₂, NH(C₁₋₃alkyl), N(C₁₋₃alkyl)₂,
 CO₂H or CO₂C₁₋₃alkyl;

R₁₁₀ is selected from hydroxy, C₁₋₃alkyl, halo, CO₂H, CO₂C₁₋₃alkyl, CN, NH₂, NH(C₁₋₃alkyl)₂,
 25 C(S)NH₂, C(S)NH(C₁₋₃alkyl) or C(S)N(C₁₋₃alkyl)₂;

n is 0 or an integer from 1 to 3;

m is 0 or an integer from 1 to 20; and

30

wherein an alkyl, alkenyl or alkyloxy, group may be optionally substituted one or more

- 129 -

times.

32. A compound according to claim 31 wherein Y is selected from -O-, -S-, -NH- or SO₃.

5

33. A compound according to claim 31 wherein R₁₀₁ is selected from hydrogen, CO₂H or CO₂C₁₋₃alkyl.

34. A compound according to claim 31 wherein R₁₀₂ is selected from from C₁₋₂₀alkyl, 10 C₂₋₂₀alkenyl, CO₂H, CO₂C₁₋₂₀alkyl, CO₂C₂₋₂₀alkenyl, CO₂(CH₂)_mCO₂H, SO₃H, SO₃C₁₋₂₀alkyl, SO₃C₂₋₃₀alkenyl, SO₃(CH₂)_mCO₂H, (CH₂)_mhydroxy, (CH₂)_mNH₂, (CH₂)_mCN or (CH₂)_mhalo.

35. A compound according to claim 31 wherein R₁₀₃ is selected from hydrogen, 15 hydroxy or methoxy.

36. A compound according to claim 31 wherein R₁₀₄ is selected from hydrogen, hydroxy, methyl, NH₂ or CH₂OH.

20 37. A compound according to claim 31 wherein R₁₀₅ is selected from hydrogen, hydroxy or methoxy.

38. A compound according to claim 31 wherein R₁₀₆ is selected from hydrogen, C₁₋₃alkyl, C(O)NH₂, C(O)NH(C₁₋₃alkyl), C(O)N(C₁₋₃alkyl)₂, C(S)NH₂, C(S)NH(C₁₋₃alkyl) or 25 C(S)N(C₁₋₃alkyl)₂.

39. A compound according to claim 31 wherein R₁₀₇ is selected from hydrogen, hydroxy, halo, cyano, NH₂, nitro or SO₃H.

30 40. A compound according to claim 31 wherein R₁₀₈ is hydrogen.

- 130 -

41. A compound of formula (I) selected from the group consisting of
- 6,7-dimethoxy-2-acetonoaphthone
- 2-carboxy-6-hydroxynaphthalene-5-sulfonic acid
- Pentyl 6,7-dihydroxy-2-naphthalenesulfonate
- 5 2,3-dihydronaphtho[2,3-b][1,4]dioxine-7-carboxylic acid
- Methyl 6-hydroxy-2-naphthoate
- dodecanyl-6-hydroxy-2-naphthoate
- [(6-hydroxy-2-naphthyl)carbonyl]oxyhexanoic acid
- (6-methoxy-6-oxohexyl)-6-hydroxy-2-naphthoate
- 10 6-hydroxy-5-nitro-2-naphthoic acid
- Ethyl 1,6-dihydroxy-2-naphthoate
- Ethyl 6-[(dimethylamino)carbonyl]sulfanyl-1-methoxy-2-naphthoate
- Ethyl 6-hydroxy-1-methoxy-2-naphthoate
- Ethyl 6-[(dimethylamino)thiocarbonyl]oxy-1-methoxy-2-naphthoate
- 15 7-methoxy-3-hydroxy-2-naphthoic acid
- Methyl 7-methoxy-3-hydroxy-2-naphthoate
- Methyl 7-methoxy-3-methyl-2-naphthoate
- 7-methoxy-3-methyl-2-naphthoic acid
- 5-bromo-6-methoxy-2-methyl-3-naphthoic acid
- 20 6-hydroxy-[2-(1-pentylamino)methyl]-3-naphthoic acid
- Methyl 3-bromomethyl-7-hydroxy-2-naphthoate
- Methyl 7-methoxy-2-naphthoate
- Methyl 7-hydroxy-2-naphthoate
- Methyl 7-hydroxy-8-nitro-2-naphthoate
- 25 Methyl 6-hydroxy-5-nitro-2-naphthoate
- Methyl 6-methoxy-5-nitro-2-naphthoate
- Methyl 5-amino-6-methoxy-2-naphthoate
- Methyl 6-methoxy-2-naphthoate
- 2-hydroxymethyl-6-methoxynaphthalene
- 30 2-bromomethyl-6-methoxy-naphthalene
- 2-cyanomethyl-6-methoxynaphthalene

- 131 -

2-(1-cyano-1-hex-5-enyl)-6-methoxynaphthalene

2-(6-methoxy-2-naphthyl)hept-6-enoic acid

Methyl 2-(6-methoxy-2-naphthyl)hept-6-enoate

7-hydroxy-2-(6-methoxy-2-naphthyl)heptanoic acid

5 Methyl 6-methoxy-8-methyl-2-naphthoate ester.